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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/726,258	11/29/2000	Vanessa Hsei	P1085R4-1AC1	4895

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EXAMINER	
ROARK, JESSICA H	

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 03/17/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/726,258	HSEI ET AL.	
	Examiner	Art Unit	
	Jessica H. Roark	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 December 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,25,26,28,29 and 31-42* is/are pending in the application.

4a) Of the above claim(s) *37,39 and 40* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 25, 26, 28, 29, 31-36, 38 and 41-42* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

RESPONSE TO APPLICANT'S AMENDMENT

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 12/22/03 has been entered.

2. Applicant's amendment, filed 12/22/03, is acknowledged.
Claims 2-24, 27 and 30 are cancelled.
Claims 37-42 have been added.
Claims 1, 25-26, 28-29 and 31-42 are pending.

Claims 37 and 39-40 stand withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected species.

Claims 1, 25-26, 28-29, 31-36, 38 and 41-42 *are under consideration in the instant application.*

3. Applicant's traversal of the withdrawal of claim 20, now claim 37, in the Remarks filed 12/22/03 is acknowledged. Applicant's traversal is on the grounds that "at least 20 kD" encompasses the species of "at least 40 kD". While rejoinder of the claims reciting at least 40 kD would be appropriate upon allowance of claims reciting "at least 20 kD", at present these claims stand rejected and rejoinder is therefore not appropriate.

4. This Office Action will be in response to applicant's arguments, filed 12/22/03.
The rejections of record can be found in the previous Office Action.

It is noted that New Grounds of Rejection are set forth herein.

Claim Rejections - 35 USC § 112 second paragraph

5. The following is a quotation of the second paragraph of 35 U.S.C. 112.

> *The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.*

6. Claims 29, 33-34, 38 and 41-42 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A) Claims 29, 38 and 41-42 are ambiguous in that it is unclear if the claims require all three complementarity determining regions (CDRs) of the recited light chains, or only require one of the three CDRs of the recited light chain. The recitation "the complementarity determining region" is ambiguous because the definite article "the" implies there is but a single CDR, whereas there are in fact three CDRS present n each of SEQ ID NOS:56 and 62. Applicant should provide claim language that clearly indicates the number of CDRs of the recited light chains that are required by the claims.

It is noted that claim 29 as originally filed recited "the complementarity determining regions", which was interpreted as requiring all three CDRs of the recited light chains.

B) Claims 33 and 34 each recite "nonproteinaceous polymer molecules" in reference to independent claim 1. However, there is a lack of antecedent basis for this limitation because claim 1 does not recite nonproteinaceous polymer molecules generally, but instead is limited to PEG.

C) Applicant is reminded that any amendment must point to a basis in the specification so as not to add new matter. See MPEP 714.02 and 2163.06.

Claim Rejections - 35 USC § 112 first paragraph

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. In view of the ambiguity regarding the number of CDRS derived from the recited light chain sequences, the following rejection is set forth;

9. Claims 29, 38 and 41-42 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for conjugates comprising Fab' fragments in which the three complementarity determining regions (CDRs) in the light chain variable region are all defined by a single antibody which binds IL-8; does not reasonably provide enablement for conjugates comprising Fab' fragments that does not comprise the three light chain CDRs defined by the amino acid sequence of a parental antibody that binds IL-8. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The specification does not provide a sufficiently enabling description of the claimed invention. The breadth of the instant claims encompass antibodies or antibody fragments thereof in which fewer than all of the three CDRs found in the light chain variable region are defined.

Applicant has disclosed multiple antibodies that bind IL-8 (e.g., pages 183-188). Humanized versions of some of these antibodies in which all three CDRs of the heavy chain variable region and all three CDRs of the light chain variable region are defined are described beginning on page 197. However, the specification does not appear to disclose antibodies in which fewer than all three CDRs of the light chain are used to confer binding to IL-8.

The state of the art recognized that it would be highly unpredictable that an Fab' fragment comprising less than all three CDRs of a light chain with a desired specificity would bind the same antigen as the parental antibody. The art recognized that the minimal structure which the skilled artisan would consider predictive of the function of IL-8 binding is a light chain in the context of a heavy chain, wherein the three CDRs of the light chain variable region are from the same parental antibody.

Reasonable correlation must exist between the scope of the claims and scope of enablement set forth. Given the recognized unpredictable nature of making antibodies with a desired specificity having fewer than all six CDRs from a reference antibody and the lack of sufficient guidance provided in the specification; the experimentation left to those skilled in the art, is unnecessarily, and improperly, extensive and undue.

Claim Rejections – 35 U.S.C. §§ 102 and 103

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

11. Claims 1, 25, 31-32 and 34-35 are rejected under 35 U.S.C. 102(b) as being anticipated by Griffiths et al. (WO 96/09325).

Griffiths et al. teach a conjugate comprising a radioantibody fragment and a PEG molecule (see entire document, e.g., Abstract). Griffiths et al. teach that the antibody can be an Fab' fragment (see, e.g., page 4 at lines 23-34). Griffiths et al. also teach that the PEG used in the conjugate may be from 1,000 to 30,000 (i.e., 1 kD to 30 kD) in size (see page 5, especially lines 6-13). Griffiths et al. also teach that the PEG may be covalently attached to the thiol group in the hinge region of the molecule (e.g., page 5 at lines 14-19). Radiolabeling of antibodies, including Fab' fragments, is also taught (e.g., pages 8-9). Formulation in a sterile carrier is taught at page 12.

Although Griffiths et al. is silent regarding the apparent and relative sizes of these conjugates, Applicant is reminded that no more of the reference is required than that it sets forth the substance of the invention. The claimed functional limitations would be inherent properties of an Fab' covalently attached to a PEG of 20 kD.

The reference teachings therefore anticipate the instant claims.

12. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

13. Claims 1, 25, 31-33 and 36 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Zapata et al. (FASEB J. 1995, Abstract #1288, 9:A1479, IDS # 98) in view of Braxton (US Pat. No. 5,766,897, IDS #20).

Applicant's arguments, filed 12/22/03, have been fully considered but have not been found convincing for the reasons of record. It is noted that the amendment filed 12/22/03 did not amend the instant claims,. and the entered amendment after final filed 7/23/03 changed only the "consisting essentially of language to "comprising", which as noted in the advisory action did not affect the rejection of record.

Accordingly, the rejection of record is incorporated herein as if set forth in full.

Applicant's new arguments focus on the fact that the references are silent regarding the apparent size of the conjugate and that the apparent size is at least about 8 fold greater than the apparent size of the antibody fragment.

Applicant argues that because these properties were not appreciated by the ordinary artisan, the ordinary artisan would not have motivated to select a PEG that was 20 kD in size for the Fab' conjugate.

However, for the reasons set forth in detail previously, the teachings of Zapata et al. in view of Braxton did provide both motivation to formulate a conjugate of an Fab' to which a PEG of 20 kD was covalently attached to the free thiol in the hinge region. In particular, Zapata et al. note that although both the 5 kD and 10 kD forms of PEG reduced serum clearance, the 10 kD form of PEG was better than the 5 kD form (see last third of Abstract). Consequently, Zapata et al. clearly recognized that increasing the size of the PEG resulted in a further reduction the clearance rate. Thus the teaching of Zapata et al. establish that the size of the PEG molecule was a variable that affected the desirable property of reducing serum clearance rates, with a larger size producing a better effect. The Examiner maintains that it would therefore have been obvious to one of ordinary skill in the art to use higher molecular weight PEGs for covalent linkage to any Fab' antibody fragment for which one desired to reduce the serum clearance rate.

Braxton teach methods for the PEGylation of proteins by attaching a PEG molecule via the thiol group on a free cysteine (see entire document, e.g., column 12 especially lines 48-50). Braxton teach that the molecular weight of the attached PEG may be from 200 to 20,000 MW (i.e., from about 0.2 to 20 kD) and that particularly for relatively small proteins that generally have short half lives and because of their small size have fewer PEG sites available, the PEG moiety used should be of a higher molecular weight (see especially lines 48-65).

The Examiner maintains that given the guidance provided by Braxton that higher molecular weight PEGs should be used when only a few coupling sites are available on relatively small proteins, such as the Fab' antibody fragments taught by Zapata et al.; and the identification by Braxton of 20 kD as being the upper end of the molecular weight range of PEGs taught; it would have been obvious to the ordinary artisan at the time the invention was made to select a 20 kD PEG for use in coupling to relatively small proteins, including the Fab' antibody fragments as taught by Zapata et al. The Examiner maintains that the ordinary artisan would have been motivated to formulate such a conjugate in order to further reduce the serum clearance of a therapeutic antibody.

Although the references are silent with respect to the apparent size of the conjugate and the relationship of the apparent size of the conjugate to that of the unconjugated Fab' fragment; given that the same product is produced (an Fab' fragment coupled to a 20 kD single chain PEG), that product would necessarily have an apparent size of at least about 500 kD and that would be at least about 8 fold greater than the apparent size of at least one antibody fragment.

The Examiner reiterates that motivation existed for substituting the 20kD PEG into the Fab'-PEG conjugate taught by Zapata et al.; thus no motivation is required for the ordinary artisan to select based upon an apparent size of at least about 500 kD and at least about 8 fold greater apparent size; motivation to select a 20kD PEG would necessarily result in these properties without any appreciation of them by the ordinary artisan.

The rejection is therefore maintained.

14. Claims 26 and 28 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Zapata et al. (FASEB J. 1995, Abstract #1288, 9:A1479, IDS # 98) in view of Braxton (US Pat. No. 5,766,897, IDS #20) as applied to claims 1, 25, 31-33 and 36 above, and further in view of Doerschuk et al (U.S. Patent No. 5,702,946, IDS #18).

Applicant's arguments with respect to the instant rejection are that Doerschuk et al. does not correct the deficiencies of Zapata et al. in view of Braxton et al.

The rejection of record is incorporated herein as if set forth in full.

Applicant's arguments regarding Zapata et al. in view of Braxton et al. have not been found convincing for the reasons set forth supra.

The rejection is therefore maintained.

15. Claims 34 and 35 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Zapata et al. (FASEB J. 1995, Abstract #1288, 9:A1479, IDS # 98) in view of Braxton (US Pat. No. 5,766,897, IDS #20) as applied to claims 1, 25, 31-33 and 36 above, and further in view of Griffiths et al (U.S. Patent No. 5,670,132, IDS #13).

Applicant's arguments with respect to the instant rejection are that Griffiths et al. does not correct the deficiencies of Zapata et al. in view of Braxton et al.

The rejection of record is incorporated herein as if set forth in full.

Applicant's arguments regarding Zapata et al. in view of Braxton et al. have not been found convincing for the reasons set forth supra.

The rejection is therefore maintained.

Conclusion

16. No claim is allowed.

17. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jessica H. Roark whose telephone number is (571) 272-0848. The examiner can normally be reached on Monday from 7:30 to 4:00, and on Tuesdays and Thursdays from 10:00 to 4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan, can be reached at (571) 272-0841. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Jessica H. Roark
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March 15, 2004

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